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Purinergic Signalling in the Kidney: physiology and disease

Marie-Louise T Monaghan[1], Matthew A Bailey[1] Robert J Unwin[2]

[1]British Heart Foundation Centre for Cardiovascular Science, The University of Edinburgh, [2]The Department of Renal Medicine, University College London, UK.

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Correspondence:

Professor Robert Unwin

Department of Renal Medicine,

UCL Medical School

Royal Free Campus

Rowland Hill Street,

London NW3 2PF,

United Kingdom

Email: robert.unwin@ucl.ac.uk

Abstract

Historically, the control of renal vascular and tubular function has, for the most part, concentrated on neural and endocrine regulation. However, in addition to these extrinsic factors, it is now appreciated that several complex humoral control systems exist within the kidney that can act in an autocrine and/or paracrine fashion. These paracrine systems complement neuroendocrine regulation by dynamically tuning renal vascular and tubular function to buffer rapid changes in nephron perfusion and flow rate of tubular fluid. One of the most pervasive is the extracellular nucleotide/P2 receptor system, which is central to many of the intrinsic regulatory feedback loops within the kidney such as renal haemodynamic autoregulation and tubuloglomerular feedback (TGF). Although physiological actions of extracellular adenine nucleotides were reported almost 100 years ago, the conceptual framework for purinergic regulation of renal function owes much to the work of Geoffrey Burnstock. In this review, we reflect on our >20-year collaboration with Professor Burnstock and highlight the research that is still unlocking the potential of the renal purinergic system to understand and treat kidney disease.

1. Introduction

Forty years after the potent effects of adenine compounds on cardiac and smooth muscle were first shown[1], the role of ATP as a non-adrenergic, non-cholinergic neurotransmitter was proposed and the term 'purinergic' coined[2]. Another five decades on and purinergic signalling has progressed from controversy to therapy, and is now a well-trodden path; the key role of Geoff Burnstock, who was in the vanguard and guided many of us along the way, is widely acknowledged and justly applauded. Our first contact with Geoff came in the early 1990s with an informal chat based on a shared interest in co-transmitters in the gut and their role in other organs, including potentially the kidney[3]. Geoff's laboratory at the time was based in the Department of Anatomy on UCL's main campus. His group had just begun cloning P2 receptors, an advance that provided improved molecular tools to allow detection and localisation of P2 receptors (P2R) in tissue samples. Tools for P2X1R were particularly good at that time and our collaboration began there. This led to the first comprehensive analysis of P2X1R expression in the kidney[4], an auspicious beginning given the important role of this receptor in renal vascular physiology and disease, which is discussed more below. This was followed by a systematic analysis of P2YR in defined nephron segments[5,6], painstakingly dissected from the rat kidney, and examination of renal nerves as a source of ATP to the glomerulus[7]. Thence, it was a short step to unravelling the functionality of P2R in physiology[8] and disease[9,10].

In 2003, Unwin, Bailey and Burnstock published a 'state-of-play' review synthesising current knowledge of the renal purinergic system[11], which at that time was largely descriptive and/or limited to cell models; potential was there but as yet unrealised. The literature has expanded enormously since then[12,13] and the concept of renal purinergic signalling is so widely acknowledged as important that it has warranted a chapter in one

of the most influential textbooks on kidney function[14]. The Burnstock vision was to leverage knowledge of the purinergic system to treat human disease. The research discussed here demonstrates that abnormal purinergic signalling can contribute to kidney disease and provides a platform for realising the therapeutic potential of this system.

2. ATP in the Kidney

Extracellular ATP is released as a paracrine/autocrine signal by many cells of the kidney and regulates various aspects of normal renal vascular and tubular physiology. Extracellular ATP is also recognised as a damage-associated molecular pattern (DAMP) signal involved in the pathophysiology of some acute renal dieases, particularly as part of the inflammatory response to abrupt tissue injury and which depends on controlling local ATP concentrations[15]. ATP, UTP and UDP are released from intracellular storage pools to the extracellular compartment by multiple cell types under inflammatory or hypoxic conditions[16]. Although it is known that ATP release can occur in an uncontrolled fashion during processes leading to cell necrosis, studies have examined the molecular pathways involved in the controlled release of extracellular ATP. These studies have been reviewed in detail elsewhere[17,18]. Briefly. inflammatory cells can release ATP via pannexins or connexin hemichannels[19,20]. Pannexins, transmembrane protein channels, act to connect the extracellular and intracellular spaces, and are thought to be involved in the controlled release of ATP from apoptotic cells[21]. Connexins have also been suggested to control ATP release from inflammatory cells and the vascular endothelium following shear stress[17].

Extracellular ATP and UTP are rapidly degraded to ADP and UDP, respectively, by catabolic enzymes, the ectonucleotidases; these breakdown products are themselves potent agonists at P2Y1,6,12,13 and 14 receptors. ADP itself can be metabolised further

by CD39 (ENTPD1) to produce 5'-AMP, before the final step in ATP breakdown to produce adenosine by CD73 (NT5E). As shown in Figure 1, P1 receptors recognize adenosine, while P2R bind di- and tri-phosphate nucleotide molecules.

ATP has been shown to have a role in the regulation of many processes fundamental to the integrated control of salt and volume homeostasis, renal autoregulation[22,23] tubuloglomerular feedback (TGF)[24,25] and epithelial solute transport in most nephron segments[26]. An important aspect is that ATP release is induced by physiological stimuli such as increased luminal flow[27], and ATP/P2 signalling emerges as a core aspect of the instrinsic renal feedback loops that influence higher order physiology. Thus, sensing of NaCl by the *macula densa* is the afferent arm of TGF: as delivery increases, *macula densa* cells swell and release ATP basolaterally as the primary effector molecule. It has been estimated that ATP concentration at the basolateral surface of the *macula densa* acn approach 10 μmol/L[28]. Even when considering the rapid nature of ATP catabolism[15], concentrations in the 10 μmol/L range would be expected to be sufficient to engage a significant physiological response.

ATP also emerges as an important effector molecule for the pressure natriuresis response, the physiological process by which increased arterial pressure induces sodium excretion to regulate extracellular fluid volume and exert long-term blood pressure control[15]. Pressure natriuresis is also mechanically initiated phenomenon with ATP at its core. Using microdialysis techniques Navar et al demonstrated a positive relationship between renal artery perfusion pressure (RPP) and ATP concentrations in the medullary interstitium[29–31]. This relationship was confirmed using ATP sensors to detect tissue levels of ATP in real-time and show a dynamic response to alterations in RPP that correlated with the ensuing natriuresis[32]. The blunting of pressure natriuresis in connexin30 knockout mice confirms that the release of ATP from renal cells is an

important part of the response[33]. A study published in 2020 using microdialysis techniques also demonstrated a positive correlation between the autoregulatory and TGF-mediated adjustments in renal vascular resistance and renal interstitial ATP concentrations, suggesting that autoregulation-dependent changes in renal vascular resistance are mediated by corresponding changes in interstitial ATP concentrations[34].

3. P2 Receptors in the kidney

Within the kidney, purinergic signalling in both renal physiology and pathophysiology is an expanding area of research. In normal physiology, P2R have been shown to be expressed in almost all segments of the nephron, vasculature and interstitial cells, while differential basolateral and apical cell membrane expression of P2R has also been reported[5,6] (Figure 2). P2R have been shown to be functionally expressed on both inflammatory cells and structural cells of the kidney, including mesangial cells and podocytes[12,35]. P2R activation on these cell types is thought to result in a range of cellular responses, including cell migration, release of chemokines or cytokines, production of reactive oxygen species, induction of apoptosis, and chloride secretion[12,18,36,37].

3.1 Vasculature

P2R are expressed across the kidney macro- and micro-vasculature and have been shown to have a strong influence on vascular function[38]. P2R subunit expression and localisation in relation to renal vascular and microvascular function has been discussed in detail elsewhere[39]. It is noteworthy that P2X1R has been identified in the vascular smooth muscle of the rat renal, arcuate and interlobular arteries, and in the afferent arteriole; P2X2R in the smooth muscle of larger renal arteries, and P2X4R in the vascular endothelium[12]. Moreover, P2X7R mRNA has been shown to be expressed under normal, non-inflammatory conditions in endothelial cells[40,41] and this receptor

has been immunolocalized to the endothelium of the pre-glomerular vasculature[42], and also shown to be expressed in the *vasa recta*[43] with functional data suggesting its activation results in contraction of renal medullary pericytes[44].

P2Y12R have been found to be highly expressed by platelets and have an established role in platelet activation, which has become a target for newer antiplatelet therapies such as clopidogrel and ticagrelor[45]. However P2Y12R has also been detected in both human and rat non-renal vascular tissue, and its expression in the cortex and outer and inner medulla in the vasculature and tubules[46]. It has been suggested that P2Y12R may have a role in controlling renal vessel tone and in tubular transport[46,47]. A recent study *in vivo* found that ADP can cause systemic and renal vasodilation, resulting in decreased mean arterial pressure, and determined that this effect was mediated partially by P2Y12R. It has been reported that P2Y12R also exert a tonic action to reduce tubular water reabsorption and thereby urinary concentrating ability[48]. Work by Kishore and colleagues localised P2Y12R at the protein level to the renal collecting duct, along with aquaporin-2. They found subsequently that administration of clopidogrel bisulphate, an irreversible inhibitor of P2Y12R, significantly increased urinary concentration and aquaporin-2 protein levels in the kidneys of Sprague-Dawley rats[46]. These findings led to the Kirshore group proposing that this mechanism might be important in the pathophysiology of cyst expansion in renal cystics diseases such as PKD.

In relation to renal pathophysiology, abnormalities in the P2R system are known to be involved in renal diseases[39], including diabetic nephropathy[49]. Long-term blood pressure regulation is reliant on normal renal function[50] making the P2 system an attractive field of hypertension research[43].

The P2R family is known to have a role in key regulatory processes within the kidney that, if disrupted, can have significant effects on renal function. Autoregulation, a vital

process in the kidney, is known to be mediated by P2X1R in the kidney. Increased renal blood flow due to an increase in systemic blood pressure is buffered by P2X1-mediated vasoconstriction in the afferent arteriole, which protects the glomerulus from pressure-induced injury. This is supported by work in P2X1R null mice that have been shown to have an attenuated pressure-induced vasoconstriction, resulting in autoregulatory failure and subsequent barotrauma[51].

P2X4R, the most abundantly expressed P2R in the vascular endothelium[52], is activated by ATP and reinforces the normal vascular vasodilatory response to shear stress[53]. P2X4R knockout mice are hypertensive and show impaired endothelial production of nitric oxide (NO) following an increase in blood flow[54]. The impaired pressure natriuresis response as a result of the defect in NO production ultimately affects blood pressure control[50].

P2X7R expression and activity correlates with glomerular injury when present on glomerular cells, including infiltrating inflammatory cells, and in models of severe hypertension and type 1 diabetes[10]. It has been shown that expression of P2X7R is upregulated in glomerular disease and in a model of acute glomerulonephritis[55], and that P2X7R-deficiency or blockade can attenuate renal injury in the experimental model[56].

3.2 Renal Tubules

The distribution of P2 receptors along the tubules and the inhibitory effect on tubular electrolyte transport have been reviewed in depth[12] and are summarised in Figure 2[39,57–59]. One of the best-established examples of intrarenal purinergic signalling is communication between tubule epithelial cells and vascular smooth muscle cells of the afferent arteriole to achieve TGF, the co-ordination of glomerular filtration rate and

tubular transport within a single nephron[58]. An increase in distal tubular sodium chloride load results in basolateral ATP release from *macula densa* cells[60] and the concentration of ATP in the cortical interstitium responds appropriately to inhibit or activate of TGF *in vivo*[61]. In most species, the *macula densa* is anatomically separated from the afferent arteriole by the extraglomerular mesangium. Thus, *macula densa*-derived ATP activates P2R to propogate a wave of calcium through the mesangium[62]. This ultimately results in afferent arteriolar constriction, engaging TGF. The release of ATP from mesangial cells and its hydrolysis to adenosine is suggested by experiments in knockout mice that show a blunted TGF response in mice lacking either adenosine A1 receptors[63] or ecto-5'-nucleotidase[64].

P2R act in a dual fashion to modulate ion transport. Secretory epithelia P2R are known to stimulate ion and water secretion, as opposed to absorptive epithelia, where P2R act to inhibit reabsorption[65]. As such, P2R stimulation can result in an increase or decrease in fluid secretion, with differing roles along the nephron. In the proximal tubule, P2Y1R in the luminal membrane inhibit HCO_3 absorption[66]. In the distal convoluted tubule, luminal nucleotides inhibit TRPV5-dependent Ca^{2+} absorption[67]. In the cortical collecting duct, luminal and basolateral nucleotides inhibit ROMK-dependent K^+ secretion[68] and ENaC-dependent Na^+ transport[65]. In the inner medullary collecting duct, basolateral nucleotides reduce aquaporin-2-dependent water transport[69]. More recently, use of designer receptors exclusively activated by designer drug (DREADD) technology in the renal tubule demonstrated that selective activation of the P2Y2 receptor and G_q signaling in principal cells of the collecting duct is sufficient to promote renal salt excretion[70].

Furthermore, recent work has suggested a role for tubular P2R and inflammasome signalling. Work by Lee et al. indicated that induction of kidney NLR family pyrin

domain containing 3 (NLRP3) inflammasome signalling after renal ischemia and reperfusion injury was significantly attenuated in P2X4 KO mice. A P2R agonist ATPγS can increase NLRP3 inflammasome signalling in isolated renal proximal tubule cells from WT mice; however, this was not observed in renal proximal tubules isolated from P2X4R knockout mice. Their findings suggested that renal proximal tubular P2X4R activation exacerbates ischemic acute kidney injury (AKI) and promotes NLRP3 inflammasome signalling[71].

4. P2 Signalling in Renal Disease.

4.1 Immune Function and Inflammation

Sustained tubule-interstitial inflammation has a key role in the development and progression of kidney disease by driving a vicious cycle of injury, fibrosis, and impaired functionality (e.g., reduced GFR and impaired pressure natriuresis response[72]). A growing literature suggests that ATP and other purine and pyrimidine nucleotides contribute to triggerng and/or sustaining inflammation in acute and chronic renal disease[73,74] by acting as ubiquitous and efficient DAMPs[75] that can activate the innate immune response[21]. Indeed, purinergic signalling is intimately involved in activation of the NLRP3 inflammasome in the kidney, leading to production of the pro-inflammatory cytokines IL-1β and IL-18, as well as pro-inflammatory cell death, pyroptosis[76]. [77]. A variety of insults, toxic and ischemic, induce renal macrophages to release ATP, leading to autocrine activation of P2X7R to stimulate the NLRP3 inflammasome and release IL-1β[78,79]. P2X7R can also stimulate inflammasome activation in a paracrine manner in response to ATP released following hypoxic injury with activation of P2X7R also having the potential to amplify ATP release from macrophages[80,81]. The role of inflammation mediated by the NLRP3 inflammasome in

the progression of CKD and its potential as a therapeutic target is an area of intense research interest at present and is considered elsewhere[82].

Approaches targeting the purinergic system are proving effective in pre-clinical models of acute and chronic renal diseases. Thus, P2X7R blockade (or P2X7R deficiency in hematopoietic cells) ameliorated renal ischemic reperfusion injury in mice due to the expansion of regulatory T-cells[83]. Apyrase treatment to scavenge extracellular ATP is similarly protective[84]. In a rat transplant model, oxidised ATP, which blocks P2X7R, protects against acute kidney allograft rejection by suppression of T cell, B cell and macrophage activity[85]. However, to sound a more cautionary note, P2 receptors are expressed in various immune cells (eosinophils, neutrophils, mast cells, monocytes/macrophages, and lymphocytes[86]) and extracellular nucleotides ican nfluence a wide number of diverse inflammatory reactions. These action are complex, and often reciprocal. In macrophages, for example, ATP/P2X7 signalling has the capacity to polarise cells into either a pro-inflammation or pro-resolution phenotype[87]. Therefore, the role purinergic signalling in progressive renal disease is not fully elucidated and the likely therepeutic potential of this system is not yet apparent.

4.2 Diabetic Kidney Disease (DKD)

DKD is the leading cause of renal failure[88] and incorporates aspects of chronic inflammation, fibrosis and remodelling with functional decline. Unsurprisingly, abnormal purinergic signalling has long been considered a contributory factor in the progression of DKD. Two major contributory pathways emerge from a large literature. First, diabetes reduces beneficial P1 receptor activation by adenosine; second, augmented extracellular ATP activates an over-expressed renal P2X7 receptor[35].

The role of the P1 receptor system in diabetes is discussed elsewhere[89]. This system is consider "beneficial" because of antithromboic and anrti-inflammatory actions of P1 activation. An important additional aspect in kidney functionality is the tonic suppression of single nephron GFR by A1 and $A2_A$ receptor activation[90]. Activation of A1R in the afferent arteriole normally leads to vasoconstriction, reducing capillary hydrostatic pressure and lowering single nephron GFR. In diabetes, A1R knockout mice have an exaggerated glomerular hyperfiltration, an early hallmark of DKD and ultimately develop more severe nephropathy[91]. Similarly, activation of $A2_AR$ causes vasodilation of the efferent arteriole, also reducing hydrostatic pressure in the glomerular capillaries and acting as a brake on single nephron GFR. In diabetic rats, this tonic control system is attenuated, contributing to glomerular hyperfiltration, an early feature of DN. Mechanistically, this mostly likely reflects reduced levels of ambient adenosine, since administration of CGS21680, an $A2_AR$ agonist, lowered single nephron GFR in diabetic animals[92], at least acutely. Chronic administration of CGS21680 also improved other hallmarks of DN, reducing proteinuria and levels of renal pro-inflammatory cytokines[93]. Such studies posit the hypothesis that diabetes attenuates adenosine/P1 signalling within key compartments of the kidney, perhaps by attenuating the activity of CD39, the pivot point controlling the balance between local P2 and P1 activation. Is there evidence to support this? CD39 knockout mice display more severe DN than wild-type controls[94]; CD39 overexpression protects against diabetes incidence in mice[95]. In humans, polymorphisms in ENTPD1, the gene encoding CD39, are associated with altered risk from DKD in African Americans with type 2 diabetes[96]. However, when assessed in cell lines, risk haplotypes increased, and protective haplotypes reduced CD39 expression[96]. This runs counter to the hypothesis but loss of CD39 seems to improve global metabolic phenotype in both mice and

humans. Thus, actions of CD39 differ between physiological systems and this adds a layer of complexity when trying to assess whether the CD39/adenosine/P1 cascade is therapeutically tractable in DKD.

The otherside of this coin is an intrarenal environment with sustained elevations in extracellular ATP, with important ramifications for P2R signalling. We previously examined renal biopsy sections from type 2 diabetics and immunolocalized P2X7R to glomeruli or glomerular mesangium. P2X7R was not expressed in non-diabetic control biopsies. Receptor activation amplified the release of MCP-1 (monocyte chemoattractant protein-1; aka CCL2) by human mesangial cells cultured in hyperglycaemic conditions[49]. This is important because enhanced mesangial secretion of MCP-1 results in macrophage accumulation and glomerular injury[97], which ultimately leads to the development of glomerular scarring and fibrosis. Indeed, elevated urinary MCP-1 to creatinine ratio has been shown to predict renal decline[98]. Whether therapeutic P2X7R antagonism can reverse DKD is unclear, but early experiments are encouraging: P2X7R knockout mice are protected from type 1 diabetes, having fewer macrophages infiltrating the glomerulus and reduced collagen IV deposition[49]. Encouraging research also comes from the diabetic rat, which identified a potentially adverse interaction between renal P2X7R and klotho, a membrane-bound protein with antioxidant and antiapoptotic properties, which is reduced in all forms chronic kidney disease[99]. An siRNA targeting P2X7R was shown to be have a beneficial on the kidneys of the streptozotocin rat model of type 1 diabetes to increase renal klotho expression and slow progression of renal injury in the model[100].

4.3 Hypertension

Genetic studies identify associations between single-nucleotide polymorphisms in genes encoding P2X4R (the loss of function variant rs28360472)[101] and P2X7R (intronic variant rs591874)[102] with incressed blood pressure. Animal studies, by us and others have provided some mechanistic insights using ANG-II-dependent hypertension as the experimental model. In this setting, Brilliant Blue G, a non-selective inhibitor of P2X4R and P2X7R restored the impaired pressure natriuresis response in the model and acutely lowered blood pressure[42]. Renal medullar perfusion and oxygenation were also acutely increased by the highly selective P2X7R antagonist AZ11657312[44]. In a series of elegant experiments, Franco and colleagues showed that chronic ANG-II induced renal over-expression of P2X1R, P2X7R, and P2X4R and provided direct evidence that acute blockade of P2X1R or P2X7R, but not P2X4R, increased single nephron GFR[103]. The effects of P2X1R, P2X7R, and AT_1R actions converge at receptor and/or post-receptor signalling pathways, but purinergic signalling exerts the dominant influence on arteriolar resistance in ANG-II-dependent hypertension[104].

These acute studies indicate that P2R antagonism, particularly P2X1R and P2X7R, can improve physiological end-points in experimental hypertension. The translational potential is supported by studies showing that prophylactic P2X7R antagonism or 'knock-out' of the murine P2X7k transcript lowers blood pressure and protects against the injury associated with experimental hypertension[105,106]; some of the anti-inflammatory effects of P2R antagonism such as reduced renal immune cell infiltration and the levels of NLPR3 activation appear to be independent of reduced blood pressure[107].

The overall picture that emerges is that a sustained increase in arterial pressure enhances ambient ATP levels in the renal interstitium that activate purinergic P2X1R and P2X7R and promote a cascade of immune cell infiltration, inflammation and renal macro- and microvascular dysfunction.

4.4 Polycystic Kidney Disease (PKD)

Autosomal-dominant polycystic kidney disease (ADPKD) is the most common inherited nephropathy and the fourth most common cause of renal failure in the Western world[108]. In a rat model of ADPKD, expression levels of P2X7R, P2Y2R and P2Y6R were found to be increased in the cystic epithelia and influence cyst growth[109]. Furthermore, epithelial cells from patients with ADPKD have been found to release higher levels of ATP when compared with healthy controls[110]. A further study noted increased levels of ATP within cyst fluid. This may reflect increased secretion from cells, but notably CD39 expression is also reduced in ADPKD patients[111], suggesting extracellular hydrolysis is impaired, prolonging P2R signalling. Finally, in a P2X7R KO zebrafish model, a reduction in cyst formation was noted. These findings suggest that P2X7R antagonism may have the potential as a drug target in the treatment of ADPKD[112]. This was shown more recently in a rat model in which findings indicated that P2X7R contributes to cyst growth by increasing pannexin-1-dependent pathogenic ATP release into the cyst lumen and a reduction in sodium transport across the cyst wall[113]. Similarly, in a mouse model of ADPKD both P2X7R and pannexin-1 were found to be abnormally increased in cyst lining cells compared with non-dilated collecting ducts. The authors also measured luminal accumulation of ATP in M1 cell renal collecting duct monolayers following treatment with the uricosuric drug probenecid, which is also a Panx1 antagonist. Their findings indicate that blockade of Panx1 can prevent release of ATP. These authors suggested that in the progression of

ADPKD, abnormally increased expression of both PANX1 and P2RX7 occurs in cyst lining epithelial cells, resulting in a pannexin1/P2X7R cooperation that leads to increased ATP release into the cyst luminal: high ATP levels are a consistently in association with cystogenesis.

5. Conclusion

Extracellular ATP and its metabolite adenosine are powerful signalling molecules that activate P2 or P1 purinergic receptors, respectively. Activation of purinergic receptors triggers multiple cascades, eliciting varied biological functions in the kidney and this processs has been shown to be dysregulated under pathophysiological conditions. There is strong pre-clinical data for targeting the purinergic system in renal disease. However, most approaches employ either knockout or prophylactic pharmacological strategies that, in the main, do not reflect the reality of clinical management of established renal disease. Similarly, it is increasinglty evident that genetic variants in P2 receptors, including P2X7R, are important experimental considerations. The pharmacogenomics of receptors and the impact of this on treatment to reduce disease progression is largely unexplored and a further obstacle to rapid clinical translation. Nevertheless, the pre-clinical studies do add value and we are beginning to gain a clearer picture of how the purinergic system operates in health and disease. The next phase of research will be to enhance our modelling of human disease, either with more chronic paradigms or using humanised models, including organoids and integrated microsystems to define key biological processes and provide a better understanding of how isoform-specific receptor antagonists can be be deployed in kidney disease. Our esteemed colleague and mentor, Professor Geoffrey Burnstock would, we are sure, agree with this and push us hard to make further progress.

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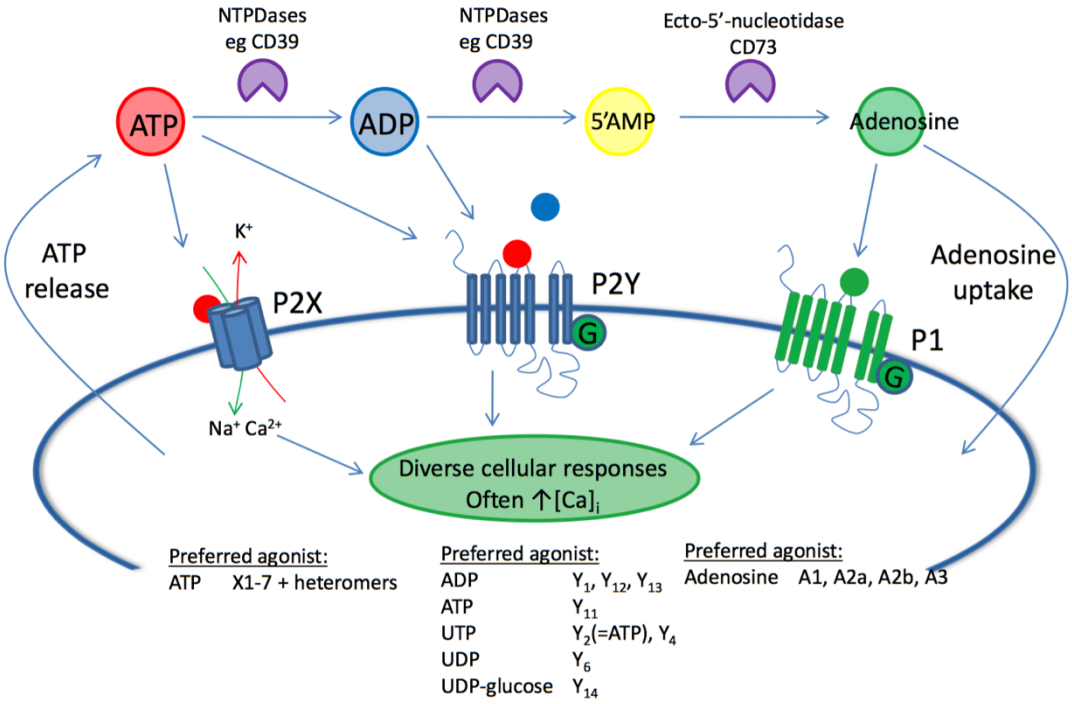
Figure Legends

Figure 1: The autocrine / paracrine purinoceptor system. In the kidney ATP release into the extracellular space is triggered by a range of stimuli including cellular stretch (sensing increase blood flow and renal tubular fluid flow), trauma, or agonist binding. Ectonucleotidases located on the plasma membrane catalyse sequential hydrolysis of ATP to ADP, 5'AMP and adenosine. P1 receptors recognize adenosine while P2 receptors bind di- and tri-phosphate nucleotide molecules. P2X receptors are non-selective cation channels with 3 protein subunits which may form homo- or heteromeric arrangements; all bind ATP. P2Y receptors are 7 transmembrane-spanning domain G-protein-coupled receptors; agonist preferences span adenosine and uracil di- and tri- nucleotides. NTPDase: ectonucleoside triphosphate diphosphohydrolase.

Figure 2: P2 Receptors in the kidney. P2Y and P2X receptor expression in the renal vasculature, glomeruli and tubules.

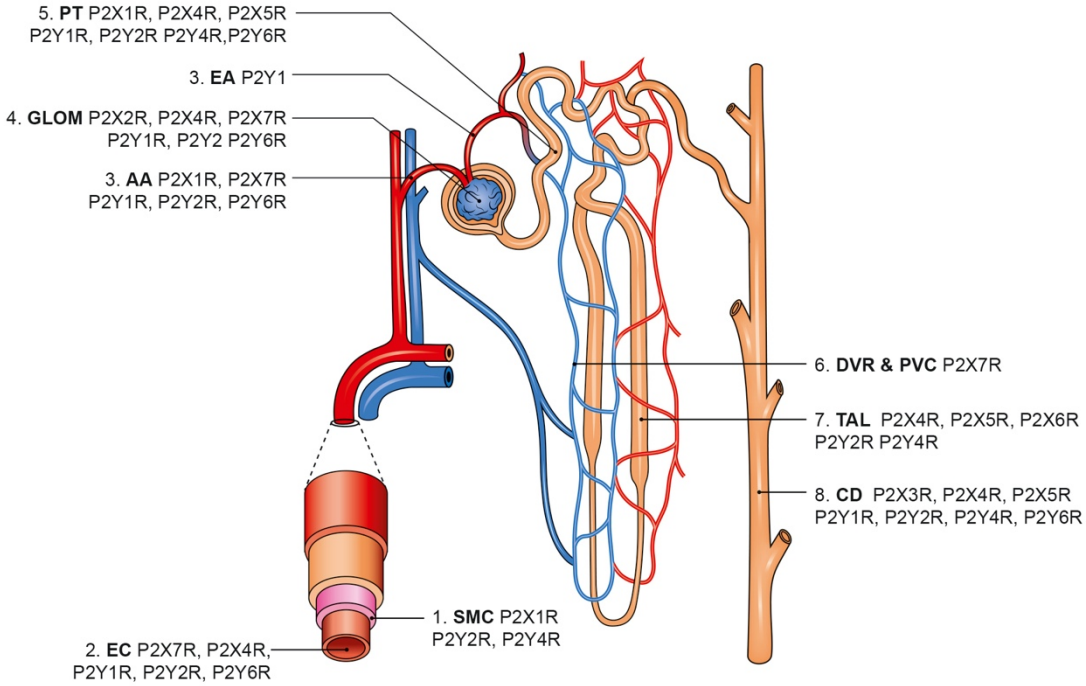


Preferred agonist:
ATP X1-7 + heteromers

Preferred agonist:

ADP	Y_1, Y_{12}, Y_{13}
ATP	Y_{11}
UTP	Y_2(=ATP), Y_4
UDP	Y_6
UDP-glucose	Y_{14}

Preferred agonist:
Adenosine A1, A2a, A2b, A3


5. **PT** P2X1R, P2X4R, P2X5R
P2Y1R, P2Y2R P2Y4R,P2Y6R
3. **EA** P2Y1
4. **GLOM** P2X2R, P2X4R, P2X7R
P2Y1R, P2Y2 P2Y6R
3. **AA** P2X1R, P2X7R
P2Y1R, P2Y2R, P2Y6R
6. **DVR & PVC** P2X7R
7. **TAL** P2X4R, P2X5R, P2X6R
P2Y2R P2Y4R
8. **CD** P2X3R, P2X4R, P2X5R
P2Y1R, P2Y2R, P2Y4R, P2Y6R
1. **SMC** P2X1R
P2Y2R, P2Y4R
2. **EC** P2X7R, P2X4R,
P2Y1R, P2Y2R, P2Y6R